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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,006	09/17/2001	Robert J. Schneider	5914-084-999	7849

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,006	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *22,24-29,31-34 and 36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24-29,31,34 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

This is a response to the amendment filed on 01/17/06. Claims 22, 29, 31, 32, 33, 34, have been amended. Claims 1-21, 23, 30, 35 have been canceled. Claims 22, 24-29, 31-34, 36-38 are pending.

Please note any ground of rejection(s) that has not been repeated is removed. Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 22 and 24-29, 31-34, 36-38 are still rejected under 35 U.S.C. 112, first paragraph on the same ground as stated in the previous Office Action on the same ground as stated in the previous office action.

3. In response to the previous Office Action, Applicants assume that the examiner's rejection is based on an alleged lack enablement for the use of any calcium inhibitor, with exception of cyclosporine, applicants point out that it is improper for limiting in vitro experiment is the first step of the in vivo experiment to the specific example presented, notwithstanding the disclosure and enablement of a broader invention. Se In re Anderson and In re Kamal.

4. Applicants submit the test for enablement is whether one reasonable skilled in the art could make and use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. The factors that can be considered in determining whether an amount of experimentation is undue have been listed in In re Wands. Applicants further point out that the specification provide in the form of guidance on how to identify a compound which modulates

HBV replication using *in vitro and in vivo* methods. Therefore, in combination of the amount literature referred to in the specification, and the high level of skill in the art, the experimentation to make and use the claimed methods through their scope is routine and thus, the full scope of the claimed methods is enabled. Applicants further argue that it is the examiner has not come forward with any specific evidence to substantiate the speculative assertion that some of the claimed calcium inhibitor may not inhibit HBV replication. It is the patent office that bears the initial burden of establishing a prima facie case of non-enablement. It is the examiner that needs to provide an affidavit specifying with particularity the support for the rejection if the examiner relies on any other facts within his personal knowledge as to why the claimed method would not be effectively inhibiting HBV replication (See 37 CFR 1.104(d)(2).

5. Applicants' argument has been fully considered, however, it is still not persuasive to overcome the rejection for the following points:

6. 1). Initially, the rejection under 112 1st paragraph enablement rejection mailed on November 29, 2004 and maintained in the previous office action mailed on July 15, 2005 is based on the notion that while being enabling for using an in vitro cell line system to demonstrate that the expression of recombinant hepatitis B virus (HBV) X protein (HBx) in cell line increase the activation of Src family tyrosine kinases, wherein the activation of the kinase, such as Pyk2, can be inhibited by calcium chelator EGTA or calcium channel poison or modulator cyclosporine A (CsA), does not reasonably provide enablement for having an in **vivo method** for treating patients infected with HBV by using any or all agents, which are able to modulate the cytosolic calcium concentration of a cells in vitro. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to made and use the invention commensurate in scope with these claims (See paragraph of 2 of office action mailed on November 29, 2004). Though applicants amend claim 22, the enablement rejected is still comply, because while being enabling for using an in vitro cell line system to demonstrate that the expression of recombinant hepatitis B virus (HBV) X protein (HBx) in cell line increase the activation of Src family tyrosine kinases, wherein the activation of the kinase, such as Pyk2, can be inhibited by calcium chelate EGTA or calcium channel poison or modulator cyclosporine A (CsA), does not reasonably provide enablement for having an in **vivo method** for inhibiting HBV viral replication in patients infected with HBV by using any or all agents that are

categorized as Ca++ modulator for the cytosolic, mitochondria calcium channel or endoplasmic reticulum calcium channel. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to made and use the invention commensurate in scope with these claims

7. Therefore, it is not correct that Applicants' assumption that the examiner's rejection is based on an alleged lack enablement for the use of any calcium inhibitor, with exception of cyclosporine. The scope of the enablement rejection is based on the in vitro enablement experiment that expression of HBV X protein increases the activation of Src kinase, which is inhibited by the calcium chelate EGTA and cyclosporine treatment in a cell line setting system, can not extrapolate the method of using it in vivo absence of enablement treating in vivo.

8. 2). The specification only teaches an in vitro examples for using Ca++ chelate EGTA or channel poison or cytosolic Ca++ modulator, CsA or BAPTA-AM to reversers the activation of Src family kinase and HBV viral DNA replication. There is no in vivo example of using CsA or EGTA or BAPTA-AM etc. as claims drafted being able to inhibit HBV viral replication taught in specification. Therefore, the specification does not provide sufficient evidence to support the broadly claimed scope of invention.

9. 3). Regarding to the applicants argument that the examiner needs to provide an affidavit specifying with particularity the support for the rejection, the examiner previously has already provided that some of the agents cited in the claims, such as skilled in the art produce significant detrimental effects in vivo. For example, verapamil, does not inhibit the HBV replication, instead, it exhibits a strong hepatotoxicity, causes liver damage and induces hepatitis (Dr. Kumar. D. in West J. Med. 1994, Vol. 160 (50), pp. 485-486, Dr. Guarascio P. Br. Med. J. 1984, Vol. 288, pp. 362-364, and Dr. Stem et al. N. Engl. J. Med. 1982, Vol. 306, pp. 612-613). In this office action, to further substantiate the rejection that the in vitro experimentation cannot extrapolated into a method using in vivo, the examiner provide more state of art taught by the expertise with ordinary skill in the art. For exemple, Yagisawa T et al. (Am. J. Neprol. 1997, Vol. 17 (5), pp. 440-444) teach that when HBV surface antigen positive patients under rental transplantation (Tx) were treated with cyclosporine and steroid, 77.8% showed hepatic dysfunction after average 17.8 months after Tx, 28% of said hepatic dysfunction patients died of liver failure due to fulminate hepatitis between 15 to 71 months after Tx. The liver functions of

remaining patients were improved after withdrawal of cyclosporine (See Abstract). Sandrini S et al. (Nephrol Dial Transplant. 1990, Vol. 5, No. 7, pp. 525-530) teach that when 14 HBsAg-positive renal transplanted patients treated with cyclosporine and steroids, eleven of them before transplantation developed sings of hepatitis (See Abstract).

10. Therefore, considering the high unpredictability of using the claimed immunosuppressive agents in patients plus many of them contains cytotoxicity in vivo, absence of the sufficient evidence of the examples to support the broadly claimed invention, the person with ordinary skill in the art would not except the method of administering any or all kinds of the claimed cytosolic calcium inhibitor is able to be used in HBV infected patients for inhibiting Hepatitis B virus replication. The rejection is therefore, maintained.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 22, 24-27, 33 and 36 are still rejected under 35 U.S.C. 102(b) as being anticipated by Frederich et al. (Z. Gastroenterol 1988, Vol. 26, pp. 265-270) on the same ground as stated in the previous Office Action.

3. Applicants traverse the rejection and argue that the legal standard of anticipation under 35 U.S.C. 102(b) is each and every element set forth in the claim is found, either expressively or inherently in a single prior art reference found, either expressly or inherently, in a single prior art reference. Verdegaal Bros. Inc. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 U.S.P.Q.Zd 1051 (Fed. Cir. 1987); Schering Com. v. Geneva Pharmaceuticals, Inc., 339 F.3d 1373, 1377, 67 U.S.P.Q.Zd 1664 (Fed. Cir. 2003); and Atlas Powder Co. v. IRECO, Inc.,190 F.3d 1342, 1347, 51 U.S.P.Q.M 1943 (Fed. Cir. 1999). In other words, there must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field

of the invention. Scrips Clinic & Research Foundation v. Genentech, Inc, 927 F.2d 1565, 1576, 18 U.S.P.Q.Zd 1896 (Fed. Cir. 1991). See also, Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 1236, 9 U.S.P.Q.Zd 1913 (Fed. Cir. 1989; çç...identical invention must be shown in as complete detail as is contained in the patent claim"). In response to the Examiner's rejection, Applicants submit that Friedrich fails to teach or fairly suggest the inhibition of HBV replication by the administration of cyclosporine to an HBV infected patient. For example, at page 268, col. 1, second full paragraph, Because Friedrich only teaches that the only patient with chronic Hepatitis B that showed any improvements following administration of cyclosporine A, did not demonstrate any improvement or modification of the levels of HBV markers such as HBs-Ag, HBe-Ag, anti- HBc-lgM, and HBV-bound DNA polymerase. The lack of change in the level of HBV markers is indicative of no inhibition of HBV viral replication, leading Friedrich to conclude that cyclosporin does not influence HBV viral activity (see page 269, Col. 2, first paragraph of the Conclusion). Therefore, as Friedrich fails to describe, much less teach, the inhibition of viral replication by administration of cyclosporin, Friedrich cannot anticipate the claimed invention and fails to anticipate the claims under 35 U.S.C. 102 (b).

4. Applicants' argument has been respectfully considered; however, it is still found unpersuasive because the limitation of "inhibiting hepatitis B virus (HBV) replication in HBV infected patient" is considered as a preamble language, rather than an active step as claim 22 drafted. Moreover, the "wherein clauses" in the dependent claims 24-27 for characterizing said agent as calcium modulators are also not an active steps of the claimed method. Because the functional characteristic of said agent in such claims inherently exist by nature of said agent. Therefore, comparing the actual active steps disclosed in the cited prior art and that in the claims, Frederich K. et al. teach to use same agent administered into the same kinds of patients, who are infected with HBV as that of the claims, the reference by Frederick K et al. still anticipates the rejected claims. Applicants are reminded that the mechanism underling the clinical beneficial is not an active step of a method. The patent office does not restrict a claimed subject matter according to its characteristics or mechanism.

5. Moreover, the citations of references by Crodoso et al. (Biochem J. 1997, Vol. 327, pp. 795-801 see Figs. 6 and 1st column of text on page 799, Fig. 7 and 1st column text on page 800), Sari NE (Biol. Chem. 1997, Vol. 378,No. 10, pp. 1163-1166, see abstract only), Evtodienko et al.

(Biochem. Mol. Biol. Int. 1995, Vol. 35, No. 5, pp. 1113-1121, see abstract) and Crompton et al. (Biochem. J. 1994, Vol. 302, (pt 1, pp. 181-185, see abstract) are just to indicate the inherent characteristic of Cyclosporine as Ca++ modulator know in the art no matter the reference of Frederich et al. does not explicitly discloses. Hence they are not considered as the second references for the rejection. To this context, the rejection is maintained.

6. New ground Rejections:

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 29 and 31 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 29 and 31 are vague and indefinite in that it is unclear whether the citation of determining an compound being able to modulate the cytosolic calcium is an active step of the claimed method of using said compound. Applicants are reminded if applicants wish to claim a method comprising the process of making the product as an active step of the claimed method of using the product, the active step of the process of making the product should be drafted as a active step rather than a process using a product made by a process.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 22, 24-27, 33, 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakanishi et al. (Inter. Med. 1998, Vol. 37, no. 6, pp. 512-22).

12. Nakanish K. et al. disclose that a 57-yeal old female patient infected with hepatitis B virus was treated with interferon plus cyclosporine A, progressively reduce the HBV DNA level and HBV markers (See Abstract) were observed.

13. Because the claimed method has same active steps as disclosed in the prior art by Nakanishi et al. the claimed invention is anticipated by the cited reference.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 7:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BAOQUN LI, MD
PATENT EXAMINER

Baoqun Li

Bao Qun Li
04/04/2006